CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

The previous claims have been replaced by a new set of claims. For the Examiner's convenience, Applicants point out new claims 39-41 correspond to claims 36-38, respectively. Applicants do not believe that new claims 39-41 introduce new matter.

Claim 36 was rejected under 35 USC §112, second paragraph, as being indefinite. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. Applicants have replaced claim 36 by new claim 39, which Applicants believe is free of all of the Examiner's concerns. Thus, new claim 39 does not use either the term "modified"

or the phrase "the amplified DNA." Moreover, new claim 39 makes clear that the entire step c) is optional, although the Examiner in the middle of the second paragraph on page 3 of the Office Action had already conceded that an optional step was intended when he said "The claim also contains the optional step of fragmenting the genes and reassembly of the genes."

Claims 36-38 were rejected under 35 USC §112, first paragraph, as lacking adequate written description and enabling support in the specification. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well.

There appears to be some confusion about the present invention, which confusion will hopefully be cleared with the following comments. In the first full paragraph on page 3 of the Office Action, the Examiner says that the instant process causes random mutagenesis that is then assayed to see whether mutants have been produced having improved properties. In response, Applicants point out that step e) of claim 39 recites "testing and identifying a mutant hydrolase having improved stereoselectivity or regioselectivity properties with respect to a substrate compared to said starting hydrolase." Accordingly, Applicants perceive no gap between the teachings in the specification and what is claimed with respect to this point.

The Examiner also says that the concentrations of Mg^{2+}, Mn^{2+} or the deoxynucleotide concentration do not appear to have been varied. In response, Applicants submit that there is no support whatsoever for the Examiner's position. Moreover, claim 39 in step b) expressly

requires "introducing one or more mutations into said starting hydrolase gene * * * by subjecting said starting hydrolase gene to a mutagenic polymerase chain reaction (PCR), wherein said mutagenic polymerase chain reaction comprises adjusting one or more parameters of the reaction * * * selected from the group consisting of the Mg^{2+} concentration of the reaction, the Mn^{2+} concentration of the reaction, the deoxynucleotide concentration of the reaction and the number of cycles of the reaction." Accordingly, there is no reason to believe that the invention involves other than this claimed feature.

In the third paragraph on page 3 of the Office Action, the Examiner gives what he apparently believes are good reasons for believing that the invention does, in fact, involve some other procedure. In that paragraph, the Examiner says, referring to the paragraph bridging pages 8-9 of the specification, that "the method of the instant invention first uses DnaseI to cleave the gene into fragments and then the fragment (sic) are mutagenized by using the conditions of conventional PCR *in vitro* without adding any PCR primers." The Examiner then notes an apparent inconsistency between the paragraph bridging pages 8-9 of the specification and the last paragraph on page 21 of the specification. In response, Applicants point out that that the paragraph bridging pages 8-9 of the specification discusses only the optional fragmentation and recombination step, i.e., ***step c)*** of new claim 39. Thus, it should also be clear that the paragraph bridging pages 8-9 of the specification and the last paragraph on page 21 of the specification are not, in fact, inconsistent since the last paragraph on page 21 of the specification relates to the mutagenic PCR, i.e., ***step b)*** of new claim 39.

With respect to the paragraph bridging pages 3-4 of the Office Action, the Examiner is again confusing the optional fragmentation and recombination step with the mutagenic PCR step. Also, regarding the Examiner's question, Applicants point out that in Example 1 the PCR product serves as the template for the mutagenic PCR.

With respect to the second paragraph on page 4 of the Office Action, Applicants point out that new claim 39 requires recombination of fragments of a) a plurality of mutated genes or b) a mixture of at least one starting gene and one mutated gene. Obviously, recombination of fragments from different genes can mutate the genes.

With respect to the third paragraph on page 4 of the Office Action, Applicants point out that the curves in Figure 1 with circles show the initial rate of reaction of the S-substrate as measured by UV absorption of released para-nitrophenol as a function of time; and the curves with squares show the same for the R-substrate.

In view of the foregoing, Applicants submit that there is no reason to believe that Applicants did not have possession of the invention when the application was filed or that the specification does not enable a person having ordinary skill in the art to make and use the invention without undue experimentation. In this regard, Applicants would remind the Examiner that the allegations in the specification must be accepted as true in the absence of reasonable

doubts supported by sound technical reasoning or evidence. *In re Marzocchi et al.*, 169 USPQ 367, 369 (CCPA 1971). Since all doubts raised by the Examiner have been shown above not to be valid, Applicants submit that both the written description and the enablement must be accepted. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claims 36-38 were rejected under 35 USC §103(a) as being obvious over either Williams et al. ("Williams"), Zhou et al. ("Zhou"), Leung et al. ("Leung"), Cadwell et al. ("Cadwell"), or Shinkai et al. ("Shinkai"). In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

According to *Manual of Patent Examining Procedure* ("MPEP") § 2143:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest ***all*** the claim limitations."

As the cited references are all insufficient in one or more of these respects, Applicants submit that none of the cited references makes out a *prima facie* case of the obviousness of the instant

claims.

The instant claims expressly require in step e) "identifying a mutant hydrolase having improved stereoselectivity or regioselectivity properties with respect to a substrate compared to said starting hydrolase." None of the cited references teaches or suggests this limitation. Accordingly, none of the cited references makes out a *prima facie* case of the obviousness of the instant claims.

Indeed, the cited references teach no more than what is acknowledged as prior art in the instant specification, i.e., that mutagenic PCR was known in principle. The present invention involves the application of mutagenic PCR to prepare mutagenic hydrolases and the testing and identification of mutated hydrolases having improved stereoselective or regioselective properties. Applicants respectfully submit that the Examiner's statement of the rejection is legally sufficient to make out a *prima facie* case of the obviousness of applying mutagenic PCR to prepare mutagenic hydrolases and the testing and identification of mutated hydrolases having improved stereoselective or regioselective properties. In particular, there is no teaching or suggestion in any of the cited references of the possibility of improving the stereoselective or regioselective properties of the starting hydrolase in this manner, and, as this is a recited requirement of the present claims, the cited references cannot render *prima facie* obvious this limitation.

Since, as noted above, a *prima facie* case of obviousness requires that the prior art "teach

or suggest ***all*** claim limitations," and the prior art cited here clearly fails in this requirement, Applicants respectfully submit that the cited references fail to render obvious the instant claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment under 37 CFR § 1.111 (11 pages total) is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below:

Date: January 2, 2003 By: Kurt G. Briscoe